Taiwan Journal of Ophthalmology 4 (2014) 28–32

Contents lists available at ScienceDirect

Taiwan Journal of Ophthalmology

journal homepage: www.e-tjo.com

Original article

Intraocular pressure changes after repeated intravitreal antivascular endothelial growth factor injections in patients with neovascular age-related macular degeneration with or without glaucoma

Tze-Yi Chan [a], Cheng-Kuo Cheng [a,b,c,*]

[a] Department of Ophthalmology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
[b] College of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan
[c] College of Medicine, National Taiwan University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 15 September 2013
Received in revised form
2 November 2013
Accepted 20 November 2013
Available online 28 January 2014

Keywords:
age-related macular degeneration
antivascular endothelial growth factor
bevacizumab
glaucoma
intravitreal injections
ocular hypertension
ranibizumab

ABSTRACT

Purpose: To investigate the long-term effects of multiple intravitreal injections on intraocular pressure (IOP) in patients with exudative age-related macular degeneration, and to determine whether this is related to a pre-existing diagnosis of glaucoma.

Methods: A retrospective study was carried out on 209 eyes in 173 patients with neovascular age-related macular degeneration who received at least three intravitreal injections of bevacizumab or ranibizumab, or both, from January 2006 to December 2012 at Shin Kong Wu Ho-Su Memorial Hospital. Sequential changes in IOP following the intravitreal injections were documented and the incidence and characteristics of the patients diagnosed with glaucoma were recorded and analyzed.

Results: Two hundred and nine eyes in 173 patients were included in this study. The mean number of injections was 10.1 (range 3–23). No significant change was found in IOP ($p = 0.41$, paired t test) and none of the patients experienced delayed ocular hypertension during the treatment course. No correlation was found between differences in IOP and the number of injections (correlation coefficient −0.086) and no significant change in IOP was found in patients with or without glaucoma ($p = 0.42$ and 0.37, respectively, paired t test). In addition, the use of drugs to lower IOP did not increase with repeated intravitreal injections in patients with glaucoma [single drug, 24 (63.2%) patients; two drugs 14 (36.8%) patients].

Conclusion: Repeated intravitreal antivascular endothelial growth factor injections of bevacizumab or ranibizumab, or both, did not increase the risk of increasing IOP in patients with exudative age-related macular degeneration, with or without glaucoma.

1. Introduction

Exudative age-related macular degeneration (AMD), which is characterized by the occurrence of a choroidal neovascular membrane in the macular area, has become one of the most common causes of severe impairment of visual function in elderly patients, including those in Asia and Taiwan. For years, intravitreal injections of antivascular endothelial growth factors (anti-VEGFs), such as bevacizumab and ranibizumab, were the main treatment regimen for exudative AMD. As exudative AMD often runs a chronic, prolonged course with frequent recurrences of choroidal neovascular membranes, multiple injections of anti-VEGFs are necessary for the care of these patients. Aside from common ocular complications such as postoperative infections, or inflammation and hemorrhage in the vitreous or conjunctiva, the possibility of prolonged ocular hypertension (OHT) has also been postulated to induce glaucoma.

Changes in intraocular pressure (IOP) after repeated intravitreal injections of anti-VEGF have been thoroughly studied since anti-VEGF treatment for exudative AMD was introduced. A transient increase in IOP has been noted after anti-VEGF treatment for exudative AMD; however, it is seldom sustained after a few weeks of observation.[1–7] The MARINA study observed no significant long-term changes in IOP after up to 2 years of follow-up.[1] The ANCHOR[2,3] and PIER[4] study groups reported a transient increase in IOP in some patients; however, it returned to baseline within a few

Conflicts of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

* Corresponding author. Department of Ophthalmology, Sing-Kong Wu Ho-Su Memorial Hospital, 95, Wen-Chang Road, Shih-Lin District, Taipei, Taiwan.
E-mail address: chengkuocheng.md@gmail.com (C.-K. Cheng).

2211-5056/$ – see front matter
http://dx.doi.org/10.1016/j.tjo.2013.11.002

hours of the injection in all cases. Nevertheless, several studies have reported a short-term[8–10] or even sustained increase[11–20] in IOP after intravitreal anti-VEGF treatment. Therefore, whether sustained OHT is a delayed complication of intravitreal anti-VEGF treatment has yet to be confirmed.

The aim of this study was to investigate whether there was a long-term effect on IOP in patients with exudative AMD who received multiple intravitreal injections at different points during treatment. We also investigated whether this was related to a pre-existing diagnosis of glaucoma.

2. Methods

This was a retrospective study conducted at Shin Kong Wu Ho-Su Memorial Hospital from January 2006 to December 2012. All the patients receiving intravitreal injections of bevacizumab or ranibizumab, or both, were informed about the drugs, including the off-label use of bevacizumab, and all agreed to the treatment. This study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Shin Kong Wu Ho-Su Memorial Hospital.

Data on 209 eyes in 173 patients with neovascular AMD who received at least three intravitreal injections of bevacizumab or ranibizumab, or both, were collected, together with the treatment course. Demographic information, systemic comorbidities, lens status, ocular surgery, number of injections, use of drugs to lower IOP, and IOP at baseline and at each visit were recorded. The endpoint was the last visit during this study period.

The patients were diagnosed with neovascular AMD based on clinical symptoms, optical coherence tomography (OCT), fluorescein angiography, and indocyanine green findings. The exclusion criteria were: glaucoma that was not well controlled before the first injection (baseline IOP >21 mmHg); previous ocular surgery complicated with OHT; polypoidal choroidal vasculopathy as diagnosed by indocyanine green angiography (ICGA) and other ocular disease including proliferative diabetic retinopathy, retinal vein or artery occlusion, uveitis and other ocular inflammatory diseases; and intraocular surgery during the course of treatment.

The intravitreal injections were performed under local anesthesia with 0.5% proparacaine hydrochloride eye drops. Before injection, the periocular skin was disinfected with 5% povidone–iodine solution and draped as per standard procedures. The intravitreal injections were performed at 3.5–4.0 mm posterior to the limbus in phakic eyes, or 3.2–3.5 mm posterior to the limbus in pseudophakic and aphakic eyes with a 30-gauge needle, with intravitreal injections of bevacizumab 2.5 mg/0.1 mL after anterior chamber tapping for 0.05 mL or intravitreal injections of ranibizumab 0.5 mg/0.05 mL after anterior chamber tapping for 0.05 mL, or both.

After the procedure, topical 0.25% chloramphenicol and 1% prednisolone were given four times a day, and Codemycin ointment (Oasis, Taipei, Taiwan; hydrocortisone acetate 0.1% + neomycin sulfate 0.05%) was given before bed for 3 days for the prophylaxis of infection and inflammation. The patients were then instructed to visit our clinic 1 week after the procedure and were followed monthly to decide whether reinjection of the anti-VEGF was necessary. The decision to reinject was based on an "as-needed" principle and the patients were advised to receive a reinjection if: (1) any subretinal fluid or cystic changes were persistent or reappeared in OCT examinations; (2) there was a marked increase in serous or hemorrhagic pigment epithelial detachment on OCT examinations; or (3) any hemorrhagic complications were noted on fundus examinations. Complete ocular examinations, including best corrected visual acuity, IOP, slit-lamp biomicroscopy, fundus ophthalmoscopy, and OCT, were performed at each follow-up visit.

IOP was recorded with a non-contact tonometer (NIDEK NT-530, NIDEK Inc., Tokyo, Japan) without local anesthesia and before the application of a mydriatic agent. Changes in IOP were identified as the difference between the IOP before and 1 week after each injection. Delayed OHT was defined as either an IOP ≥22 mmHg at two consecutive visits with an increase from baseline >6 mmHg, or a single IOP increase of >26 mmHg with concomitant initiation or increase in the use of IOP-lowering treatment. Changes in IOP were analyzed with paired *t* tests.

The patients were then divided into subgroups of those with glaucoma and those without glaucoma. Glaucoma was diagnosed based on funduscopy and OCT evidence of optic disc or retinal nerve fiber layer (RNFL) structural abnormalities or visual field damage consistent with retinal nerve fiber layer damage, or both. Only eyes with neovascular AMD that received intravitreal injections were taken into consideration. Changes in IOP between the patients with and without glaucoma were analyzed with independent *t* tests. The incidence and characteristics of the patients diagnosed with glaucoma, demographic data, and sequential IOP changes following the intravitreal injections were analyzed.

3. Results

Two hundred and nine eyes in 173 patients were included in this study. In total, 2132 injections of anti-VEGF were performed, including 2071 injections of bevacizumab and 61 injections of ranibizumab. One hundred and eighty eyes received intravitreal injections of bevacizumab monotherapy, and 29 eyes received both intravitreal injections of bevacizumab and ranibizumab sequentially. The mean age of the patients was 65.3 years (range 58–82 years) and 73 (34.9%) were men. A total of 70.3% of eyes were in patients with hypertension and 26.8% were in patients with diabetes mellitus. The mean number of injections was 10.1 (range 3–23). Table 1 summarizes the demographic data for the patients. There was no significant change in IOP ($p = 0.41$, paired *t* test) and none of the patients experienced delayed OHT during the treatment course. There was no correlation between the difference in IOP and the number of injections (Fig. 1; correlation coefficient −0.086).

Thirty-eight of the 209 (18.2%) eyes were diagnosed with open angle glaucoma. The pre-injection mean ± standard deviation IOP was 15.3 ± 2.43 mmHg in the patients with glaucoma, and 13.2 ± 3.47 mmHg in the patients without glaucoma. The mean numbers of injections were 9.1 and 10.3 in the patients with and without glaucoma, respectively. The changes in IOP were +0.28 ± 0.74 mmHg in the patients with glaucoma, and +0.26 ± 0.81 mmHg in the patients without glaucoma. No significant change in IOP was found in either group (glaucoma group $p = 0.42$; without glaucoma group $p = 0.37$; paired *t* test).

The use of IOP-lowering drugs did not increase with repeated intravitreal injections. An increase in IOP was not found in both

Table 1
Demographic data for all 209 eyes in this study.

Characteristic	Patients ($n = 173$)	Eyes ($n = 209$)
Age (y), mean (range)	65.3 (58–82)	64.8 (58–82)
Male sex, *n* (%)	62 (35.8)	73 (34.9)
Comorbidity, *n* (%)		
Hypertension	124 (71.7)	147 (70.3)
Diabetes mellitus	44 (25.4)	56 (26.8)
Lens status, *n* (%)		
Phakic		102 (47.7)
Pseudophakic		112 (52.3)
Glaucoma, *n* (%)	27 (15.6)	39 (18.2)
No. of injections, mean (range)		10.2 (3–23)

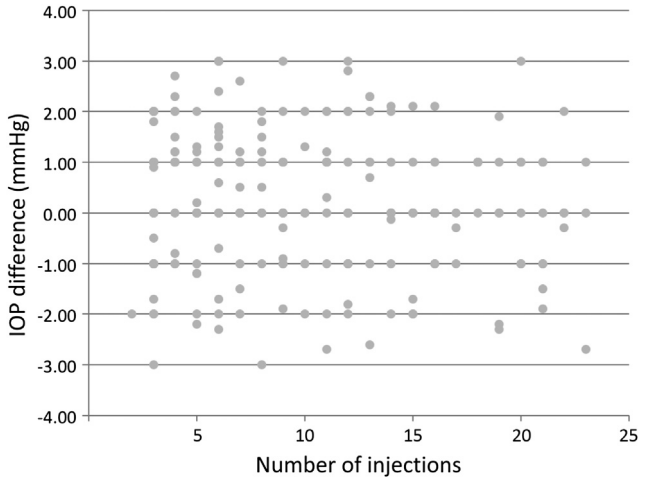

Fig. 1. Plot of difference in intraocular pressure versus number of injections showing that there was no correlation between these two variables (correlation coefficient −0.086). IOP = intraocular pressure.

groups. The drug treatment for IOP control in patients with glaucoma did not increase during the treatment, which implied that the status of glaucoma was stationary, including changes in IOP, cupping/disc (C/D ratio), or RNFL. Table 2 shows the characteristics of the patients diagnosed with glaucoma compared with those without glaucoma.

4. Discussion

In this retrospective study of 209 eyes (173 patients) treated for exudative AMD with intravitreal anti-VEGF injections (bevacizumab or ranibizumab, or both), we did not find a significant increase in IOP in the patients either with or without pre-existing glaucoma. In addition, no patient had OHT (defined as IOP ≥22 mmHg on at least two consecutive visits with an increase from baseline >6 mmHg or an IOP spike >26 mmHg). Furthermore, there was no correlation between the number of injections and the mean increase in IOP after anti-VEGF injection (Fig. 1).

Our results are consistent with previous large-scale prospective randomized clinical trials such as the MARINA and ANCHOR studies that did not report any cases of delayed OHT in patients receiving monthly injections of ranibizumab over 2 years for exudative AMD.[1–3] A recent study conducted by Wehrli et al[21] also reported a lack of delayed increase in IOP in eyes treated with anti-VEGF (bevacizumab or ranibizumab, or both) compared with the untreated fellow eyes in patients with exudative AMD. As in the current study, these workers also compared patients with a previous diagnosis of glaucoma (32 eyes) and those without glaucoma (270 eyes) and found that there was no significant difference in the incidence of delayed OHT in either group. Another study conducted by Sobaci et al[22] also reported no significant difference in the increase in IOP or changes in the nerve fiber layer in patients with exudative AMD treated with anti-VEGF compared with untreated control eyes.

Table 2
Demographic data of the patients with and without glaucoma. All the patients were followed up for at least 6 months after the latest treatment.

Characteristics	With glaucoma	Without glaucoma
No. of eyes (%)	38 (18.2%)	171 (81.8%)
IOP before injection (mmHg), mean ± SD	15.3 ± 2.43	13.2 ± 3.47
Final IOP change (mmHg), mean ± SD	+0.28 ± 0.74	+0.26 ± 0.81
p	0.42	0.37
No. of drugs for IOP control (per eye)		
Initial, mean ± SD	1.42 ± 0.52	None
Final, mean ± SD	1.47 ± 0.49	None
p	0.89	N.A.
Transient increase in IOP	None	None
No. of injections, mean ± SD (range)	9.1 ± 4.52 (3–19)	10.3 ± 5.82 (3–23)

IOP = intraocular pressure.

However, whether or not an increased incidence of delayed OHT or a gradual increase in mean IOP exists in patients treated with repeated injections of anti-VEGF is controversial. Since the beginning of the use of anti-VEGF for the treatment of exudative AMD, persistent OHT after repeated intravitreal injections has been reported in several anecdotal case reports. Kahook et al[11] reported persistent OHT in six patients treated with single or multiple intravitreal bevacizumab injections for exudative AMD (five patients) and myopic choroidal neovascular membrane (one patient). Bakri et al[12] reported four patients with persistent OHT in the range 30–50 mmHg after intravitreal ranibizumab injections for exudative AMD who required control with ocular antihypertensive drugs.

Several larger retrospective studies have reported the frequency of sustained OHT in patients with exudative AMD treated with anti-VEGF to be between 3.45% and 11.6% according to different definitions of persistent OHT and the duration of follow-up.[13–19] Adelman et al[13] reported that of 116 patients with exudative AMD without a history of glaucoma or OHT, four (3.45%) were found to have persistent OHT (IOP >21 mmHg in 2 separate measurements) from 3 to 36 months after repeated intravitreal injections of bevacizumab or ranibizumab, or both. Choi et al[15] reported an incidence of 5.5% (7 in 127 patients) of sustained increased IOP (defined as IOP >25 mmHg on 2 separate visits requiring drugs for glaucoma, or surgery) in patients with exudative AMD treated with anti-VEGF (ranibizumab, bevacizumab, or pegaptanib, or a combination of these drugs) during a follow-up period ranging from 30 days to 1759 days.

Tseng et al[16] identified 21 eyes of 19 patients with exudative AMD with a sustained increased IOP (using a definition of IOP >21 mmHg detected during at least 2 consecutive clinic visits or an increase in IOP requiring treatment, or both), which represented 3.4% of the total number of patients (555 patients) with exudative AMD treated with anti-VEGF at the doctor's clinic over a period of 62 months. Hoang et al[18] initially reported a frequency of 11.6% of persistent OHT (>5 mmHg increase from baseline IOP on two consecutive visits) in 207 patients followed from 48.1 to 260.0 weeks. The same study group[19] later reported a 7.1% rate of sustained increased IOP (defined as an absolute IOP >25 mmHg, increase above baseline >10 mmHg, or IOP of >21 mmHg and increase of >5 mmHg) in 449 eyes of 328 patients with exudative AMD treated with anti-VEGF from 66.3 to 262.7 weeks.

The mean IOP has also been reported to be increased after intravitreal anti-VEGF injections for exudative AMD. In a retrospective study of 320 patients with exudative AMD treated with intravitreal ranibizumab, Menke et al[20] found a small but significant increase (0.8 ± 3.1 mmHg) in IOP after a mean of 13.0 ± 8.0 injections over a mean follow-up period of 22.7 ± 14.1 months. However, they did not identify any patient with a final IOP >25 mmHg in their series.

Pre-existing or concurrent glaucoma has been proposed to be a possible reason for persistent OHT after repeated anti-VEGF injections for exudative AMD. In the six patients with persistent OHT reported by Kahook et al,[11] three had a previous history of glaucoma and another patient had current evidence of glaucomatous cupping and visual field defect. Good et al[14] also reported that in 216 eyes treated with anti-VEGF for exudative AMD, the patients

with pre-existing glaucoma experienced higher rates of increased IOP than patients without pre-existing glaucoma (33% vs. 3.1%, respectively; $p < 0.001$). They suggested the possibility of a heightened risk of a further increase in IOP in patients with pre-existing glaucoma who receive either bevacizumab or ranibizumab.

The connection of persistent OHT with pre-existing glaucoma has not been supported by other studies, however. None of the patients with persistent OHT reported by Bakri et al[12] and by Adelman et al[13] had a previous ocular or family history of glaucoma, suspected glaucoma, OHT, or asymmetric IOP. In the case series of Tseng et al,[16] 20 of 25 eyes that were identified as having persistent OHT were not associated with a prior history of glaucoma or prior intravitreal corticosteroid injection. Neither our series nor the series of Wehrli et al[21] found an increased risk of sustained increased IOP or increased number of drugs for glaucoma in patients with a prior history of glaucoma. Thus it is possible that a prior history of glaucoma may not be an important factor in inducing persistent OHT in patients with AMD treated with anti-VEGF injections.

The possible mechanisms for persistent OHT in patients with exudative AMD after repeated intravitreal anti-VEGF injections are still not well understood. One possible mechanism is direct damage of the trabecular meshwork by anti-VEGF treatment. However, this mechanism was not supported by a study in which no toxic effect of bevacizumab was found on cultured human trabecular meshwork cells.[23] Another proposed mechanism is intraocular inflammation such as anterior uveitis and trabeculitis.[12] Severe uveitis was found in 1.3% of patients in the MARINA study, and episodes of mild to severe acute intraocular inflammation were found in up to 10% of patients with AMD treated with monthly 0.5 mg ranibizumab intravitreal injections in the 2-year ANCHOR study.[3]

In a retrospective cohort study of 193 eyes receiving a total of 693 bevacizumab intravitreal injections, nine patients were found to have serious acute intraocular inflammation, of whom one patient developed inflammation-induced glaucoma which required surgical intervention.[24] Sniegowsky et al[25] also reported a patient with a sustained increase in IOP after intravitreal injections of bevacizumab and ranibizumab which was associated with trabeculitis. As most patients do not routinely receive a complete slit-lamp examination on the 1st day after an intraocular injection in clinical practice or even in clinical trials,[1,2] it is possible that the incidence of transient intraocular inflammation may be more prevalent than previously reported. Repeated transient intraocular inflammation may progressively damage the trabecular meshwork and subsequently cause sustained OHT in patients receiving multiple intravitreal anti-VEGF injections. A third possible mechanism is an obstructing effect of small particles on the trabecular meshwork. Several workers have found that small silicone oil microdroplets or protein aggregates may develop in bevacizumab repackaged by local pharmaceutical companies.[26–29] Other mechanisms may include trabecular damage as a result of repeated IOP spikes or repeated trauma by intravitreal injection procedures.

There are several possible explanations for the lack of delayed OHT or increased mean IOP in our patients with AMD treated with intravitreal anti-VEGF injections. One possibility is the use of short-term postoperative topical corticosteroids for the prevention of injection-associated transient intraocular inflammation. We routinely prescribed topical 0.1% prednisone acetate four times a day for patients to use for 3 days after the procedures. This may have helped to prevent repeated transient inflammation after injection and the subsequent development of sustained increased IOP.

Another possibility is that delayed OHT may be induced by the accumulative effect of mechanisms causing trabecular meshwork obstruction, or damage caused after a large number of injections. This theory is supported by recent studies conducted by Hoang et al[18,19] in which treatment with a larger number of injections was associated with a significantly increased odds ratio of sustained increased IOP, especially in the patients who received more than 29 injections for exudative AMD. Tseng et al[16] also noted that large increases in IOP were more often seen after many cumulative injections (>20). In the current study, the maximum number of intravitreal injections was 23, which may not be enough to develop an increased mean IOP or delayed OHT. However, Good et al[14] did not find an association between the occurrence of delayed OHT and the number of injections. Other studies have reported persistent OHT after one to two injections[12] or after an average of four to five injections.[11,14] In the study conducted by Mencke et al,[20] although there was a trend of an increase in IOP with a longer follow-up period, there was no significant correlation between the number of injections and an increase in IOP.

Another possible explanation for the lack of increased IOP or sustained OHT in our study is that we did not use repackaged bevacizumab which may have been altered by the microaggregation of small particles such as silicone droplets or proteins. All of our bevacizumab injections were freshly drawn from a new vial that had not been repackaged or stored for more than 4 hours. This may have effectively prevented the accumulation of small particles which may accumulate and obstruct the trabecular meshwork.

The possibility of cumulative IOP spikes may also have been prevented by our method of pre-injection anterior chamber aspiration with an aqueous aliquot. Although we used 0.1 mL of bevacizumab instead of the usual 0.05 mL used by most workers, the pre-injection anterior chamber tapping may have essentially counterbalanced possible IOP spikes immediately after the intravitreal injections of bevacizumab.

The percentage of pre-existing glaucoma in our study (18.2%) was much higher than the prevalence of glaucoma in the general Asian population of people older than 50 years, which has been reported to be around 3.2% to 3.7%.[30,31] According to a pilot study in 2006, the prevalence of glaucoma in people older than 60 years was only 4.4% in Taiwan.[32] Higher prevalence was also found in the studies of Good et al[14] (21/215 eyes; 9.8%) and Wehrli et al[21] (32/302 eyes, 10.6%). As there is no report of a higher prevalence of glaucoma in exudative patients with AMD, further larger scale studies are needed to elucidate this issue.

The limitations of this study include its retrospective nature, the small number of injections, and the relatively small number of patients. However, our follow-up protocol of patients with exudative AMD treated with anti-VEGF required strict monthly follow-up visits with complete ocular examinations, including IOP measurements, until a lack of recurrence of disease activity was noted for more than 6 months. Only then was the follow-up schedule extended to 2-month to 3-month intervals. We believe this strategy may have minimized undiscovered cases of increased IOP, thus making our findings closer to a real-life situation.

In conclusion, the findings of the current study of a population of Taiwanese patients with exudative AMD showed that repeated intravitreal anti-VEGF injections of bevacizumab or ranibizumab, or both, did not increase the risk of increased IOP whether or not the patients had glaucoma. As there is still lack of consistency as to whether or not an increase in mean IOP or sustained OHT is a consequence of repeated intravitreal injections, further larger scale prospective studies are needed to clarify this conclusion.

References

1. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419–1431.

2. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432–1444.
3. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology*. 2009;116:57–65. e55.
4. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol*. 2008;145:239–248.
5. Boyer DS, Heier JS, Brown DM, Francom SF, Ianchulev T, Rubio RG. A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration. *Ophthalmology*. 2009;116:1731–1739.
6. Schmidt-Erfurth U, Eldem B, Guymer R, et al. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. *Ophthalmology*. 2011;118:831–839.
7. Holz FG, Amoaku W, Donate J, et al. Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. *Ophthalmology*. 2011;118:663–671.
8. Mojica G, Hariprasad SM, Jager RD, Mieler WF. Short-term intraocular pressure trends following intravitreal injections of ranibizumab (Lucentis) for the treatment of wet age-related macular degeneration. *Br J Ophthalmol*. 2008;92:584.
9. Gismondi M, Salati C, Salvetat ML, Zeppieri M, Brusini P. Short-term effect of intravitreal injection of Ranibizumab (Lucentis) on intraocular pressure. *J Glaucoma*. 2009;18:658–661.
10. Sharei V, Hohn F, Kohler T, Hattenbach LO, Mirshahi A. Course of intraocular pressure after intravitreal injection of 0.05 mL ranibizumab (Lucentis). *Eur J Ophthalmol*. 2010;20:174–179.
11. Kahook MY, Kimura AE, Wong LJ, Ammar DA, Maycotte MA, Mandava N. Sustained elevation in intraocular pressure associated with intravitreal bevacizumab injections. *Ophthalmic Surg Lasers Imaging*. 2009;40:293–295.
12. Bakri SJ, McCannel CA, Edwards AO, Moshfeghi DM. Persisent ocular hypertension following intravitreal ranibizumab. *Graefes Arch Clin Exp Ophthalmol*. 2008;246:955–958.
13. Adelman RA, Zheng Q, Mayer HR. Persistent ocular hypertension following intravitreal bevacizumab and ranibizumab injections. *J Ocul Pharmacol Ther*. 2010;26:105–110.
14. Good TJ, Kimura AE, Mandava N, Kahook MY. Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents. *Br J Ophthalmol*. 2011;95:1111–1114.
15. Choi DY, Ortube MC, McCannel CA, et al. Sustained elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab, and pegaptanib. *Retina*. 2011;31:1028–1035.
16. Tseng JJ, Vance SK, Della Torre KE, et al. Sustained increased intraocular pressure related to intravitreal antivascular endothelial growth factor therapy for neovascular age-related macular degeneration. *J Glaucoma*. 2012;21:241–247.
17. Mathalone N, Arodi-Golan A, Sar S, et al. Sustained elevation of intraocular pressure after intravitreal injections of bevacizumab in eyes with neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 2012;250:1435–1440.
18. Hoang QV, Mendonca LS, Della Torre KE, Jung JJ, Tsuang AJ, Freund KB. Effect on intraocular pressure in patients receiving unilateral intravitreal anti-vascular endothelial growth factor injections. *Ophthalmology*. 2012;119:321–326.
19. Hoang QV, Tsuang AJ, Gelman R, et al. Clinical predictors of sustained intraocular pressure elevation due to intravitreal anti-vascular endothelial growth factor therapy. *Retina*. 2013;33:179–187.
20. Menke MN, Salam A, Framme C, Wolf S. Long-term intraocular pressure changes in patients with neovascular age-related macular degeneration treated with ranibizumab. *Ophthalmologica*. 2013;229:168–172.
21. Wehrli SJ, Tawse K, Levin MH, Zaidi A, Pistilli M, Brucker AJ. A lack of delayed intraocular pressure elevation in patients treated with intravitreal injection of bevacizumab and ranibizumab. *Retina*. 2012;32:1295–1301.
22. Sobaci G, Gungor R, Ozge G. Effects of multiple intravitreal anti-VEGF injections on retinal nerve fiber layer and intraocular pressure: a comparative clinical study. *Int J Ophthalmol*. 2013;6:211–215.
23. Kernt M, Welge-Lussen U, Yu A, Neubauer AS, Kampik A. Bevacizumab is not toxic to human anterior- and posterior-segment cultured cells. *Ophthalmologe*. 2007;104:965–971.
24. Johnson D, Hollands H, Hollands S, Sharma S. Incidence and characteristics of acute intraocular inflammation after intravitreal injection of bevacizumab: a retrospective cohort study. *Can J Ophthalmol*. 2010;45:239–242.
25. Sniegowski M, Mandava N, Kahook MY. Sustained intraocular pressure elevation after intravitreal injection of bevacizumab and ranibizumab associated with trabeculitis. *Open Ophthalmol J*. 2010;4:28–29.
26. Bakri SJ, Ekdawi NS. Intravitreal silicone oil droplets after intravitreal drug injections. *Retina*. 2008;28:996–1001.
27. Scott IU, Oden NL, VanVeldhuisen PC, Ip MS, Blodi BA, Antoszyk AN. SCORE Study Report 7: incidence of intravitreal silicone oil droplets associated with staked-on vs luer cone syringe design. *Am J Ophthalmol*. 2009;148:725–732. e727.
28. Kahook MY, Liu L, Ruzycki P, et al. High-molecular-weight aggregates in repackaged bevacizumab. *Retina*. 2010;30:887–892.
29. Liu L, Ammar DA, Ross LA, Mandava N, Kahook MY, Carpenter JF. Silicone oil microdroplets and protein aggregates in repackaged bevacizumab and ranibizumab: effects of long-term storage and product mishandling. *Invest Ophthalmol Vis Sci*. 2011;52:1023–1034.
30. Kim JH, Kang SY, Kim NR, et al. Prevalence and characteristics of glaucoma among Korean adults. *Korean J Ophthalmol*. 2011;25:110–115.
31. Wang YX, Xu L, Yang H, Jonas JB. Prevalence of glaucoma in North China: the Beijing Eye Study. *Am J Ophthalmol*. 2010;150:917–924.
32. Chiou T-S, Johnson GJ. The prevalence of glaucoma in an urban Chinese population in Taiwan: a pilot study. *ACTA Societatis Ophthalmologicae Sinicae*. 2006;45:63–75.